SYNTHESIS OF SOME NOVEL PYRAZOLE DERIVATIVES USING 4-FORMYLPYRAZOLES AS SCAFFOLD

SYNOPSIS

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DOCTOR OF PHILOSOPHY
IN
CHEMISTRY

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SYNOPSIS

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1. Title: SYNTHESIS OF SOME NOVEL PYRAZOLE DERIVATIVES USING 4-FORMYLPYRAZOLES AS SCAFFOLD

2. Introduction

The pyrazole scaffold is present in a variety of leading marketed non-steroidal anti-inflammatory agents (Bekhit et al 2008) and several derivatives have also been found to possess a wide range of bioactivities, such as antihypertensive (Demirayak et al 2004), antibacterial (Yu et al 2015), anticonvulsant (Viveka et al 2015), antidepressant (Aziz et al, 2009), anticancer (Balbi et al 2011) and many others. Pyrazoles with various functional groups at position-4 such as aldehyde, carboxylate etc. (Sridhra et al 2004, Parmar et al 2012, Rajput and Rajput 2011, Rao et al 2017, Khloya et al 2013, Kumar et al 2007) have been known to show good pharmaceutical activities. Conversion of 4-formylpyrazoles into various 4-functionalpyrazoles such as (4-cyano, 4-COOH, oxime, amide, thiamide etc.) is well documented. A lot of organic reaction on aldehyde group is also well documented in the literature. Some of them we have discussed here.

The base-catalyzed reaction of an aldehyde with a nitroalkane (nitroaldol condensation) that was discovered by Henry more than a century ago (Henry 1895) continues to attract synthetic interest for its versatility and operational simplicity. The nitro-aldol reaction affords a powerful synthetic tool in organic synthesis for carbon-carbon bond formation between aldehydes and nitroalkanes (Soengas and Silva 2013). The Henry reaction is one of the most important atom economical methods for the formation of the C–C bond in organic chemistry (Luzzio 2001) and the resulting products such as chiral β-nitroalcohols are very important intermediates and can be further

transformed into other useful derivatives, such as carboxylic acids and amino alcohols in the synthesis of relevant biologically active compounds. In addition, chiral β-nitroalcohols are relevant building blocks in organic synthesis to form more complex structures, such as natural products (Blay et al 2010, Guo and Deng 2011, Gogoi et al 2005).

Nitro-containing compounds are synthetically important because the nitro group can be converted into several functional moieties such as the carbonyl and amine groups (Ono 2001). The transformation of a nitro group into a carbonyl group is known as the Nef reaction, which is widely used in organic synthesis (Ballini and Petrini 2004). Nitro compound can be converted into a carbonyl derivative by oxidizing reagents such as $KMnO_4$ (Shechter and Williams 1962), m-chloroperoxybenzoic acid (MCPBA) (Aizpurua 1987), hydrogen peroxide (Olah et al 1980), ozone (McMurry 1974), dimethyldioxirane (Adam 1998) and tetrapropylammonium perruthenate (Tokunaga 1995).

The Mannich reaction between a Schiff base and a nucleophile, first introduced in the early part of the 20^{th} century (Mannich and Krosch 1912) is one of the most powerful reactions known to chemists for the construction of nitrogen-containing compounds (Arend et al 1998). The aldehydes or formaldehydes are usually derivatized into N-Mannich bases since these molecules exhibit higher lipophilicity and absorption behavior than the parent aldehyde, thus making them favorable prodrugs under physiological conditions (Bundgaard and Johansen 1980). Mannich and aldol reactions are very similar, therefore, Bronsted bases should be also good catalysts for the Mannich reaction of unfunctionalized ketones via the enolate mechanism (Guo and Zhao 2013).

The Shapiro reaction has been widely applied in the synthesis of natural products, (Zhu and Cook 2012) and for the preparation of polysubstituted alkenes (Fabris 1999), many of which are not easily accessed by other means. A prototypical Shapiro reaction involves the condensation of an N-sulfonyl hydrazide with a ketone to provide a sulfonyl hydrazone, treatment of the sulfonyl hydrazone with a base to provide a vinyllithium intermediate and trapping of the vinyl anion with H^+ to afford an alkene-based product (Chamberlin and Bloom 1990).

Literature survey revealed that a number of organic reactions may be conducted on 4-formylpyrazole scaffolds for synthesis of more derivatives therefore, we decided the following objectives:

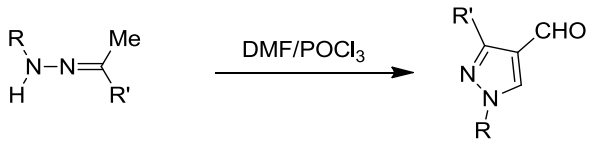
i. Synthesis, isolation and characterization of (Pyrazol-4-yl)-2-nitroalcohols using Henry reaction.
ii. Synthesis, isolation and characterization of (Pyrazol-4-yl)-2-hydroxyaldehydes/ketones using Nef reaction.
iii. Conversion of Pyrazol-4-carbaldehydes into (Pyrazol-4-yl)ethanone using Grignard reaction.
iv. Synthesis, isolation and characterization of 3-substituted amino-1-(pyrazol-4-yl)propan-1-ones using Mannich reaction.
v. Synthesis, isolation and characterization of 4-vinylpyrazoles using Shapiro reaction.
vi. Study of Heck reaction on 4-vinylpyrazoles.
vii. Evaluation of biological activities of new compounds.

3. Expected new knowledge

A lot of organic reactions on aldehyde is well documented in the literature. The literature also indicated the various significant pharmacological and medicinal activities of pyrazole derivatives. This gives us an opportunity to explore some organic reactions on 4-formylpyrazole scaffolds. Therefore, our studies are focused towards the synthesis of 4-substituted pyrazoles with various organic reactions on 4-formylpyrazoles and used them for their biological evaluation. The synthesized final targets may prove better scaffold for further synthesis of pyrazole based drugs.

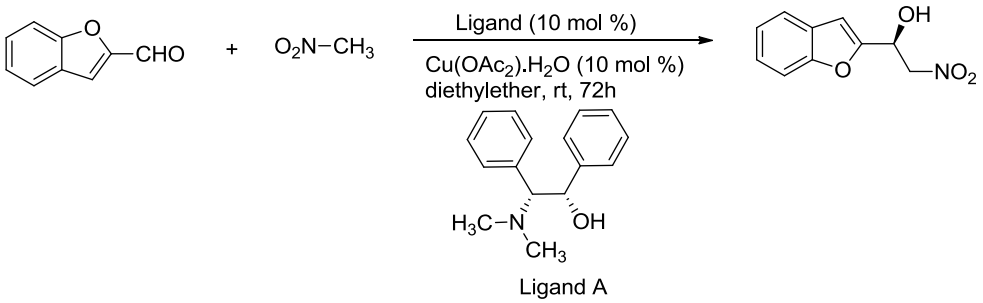
4. Review of literature

The Vilsmeier-Haack reaction is a common method for the synthesis of 4-formyl pyrazoles (Singh et al 2005, Arbaciauskiene et al 2011, Parmar et al 2012, Rajput and Rajput 2011, Rao et al 2017, Lebedev et al 2005 and Kumar et al 2007). Literature survey reveals that hydrazones of aliphatic and aromatic methyl ketones yield pyrazole-4-carbaldehydes upon diformylation on treatment with Vilsmeier-Haack reagent **(Scheme 1)**.



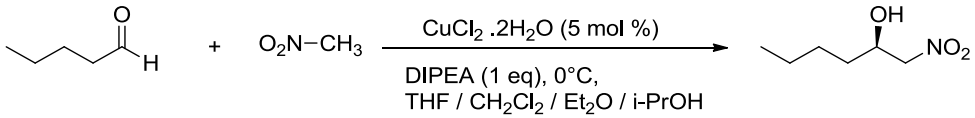
Scheme 1

Chen et al (2017) reported a kind of Henry reaction in which benzofuran-2-carbaldehyde was used as the model substrate and nitromethane was used as nucleophile with asymmetric induction of a ligand. Then the reaction was carried out in the presence of catalyst (10 mol %) which was *in situ* generated from the coordination of the ligand A with $Cu(OAc_2).H_2O$ in diethyl ether at room temperature **(Scheme 2)**.



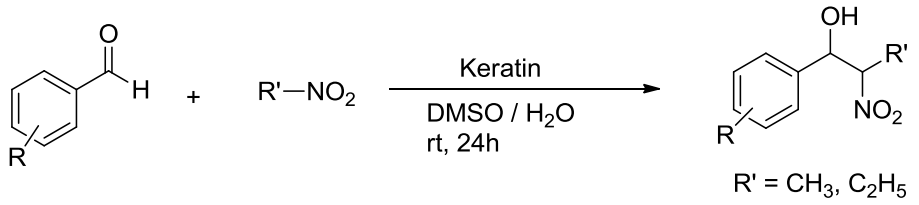
Scheme 2

Fillippova et al (2015) promoted the nitroaldol reaction between valeraldehyde and nitromethane in the presence of $CuCl_2.2H_2O$ (5 mol %) at 0°C with DIPEA (1 eq) as base additive **(Scheme 3)**.



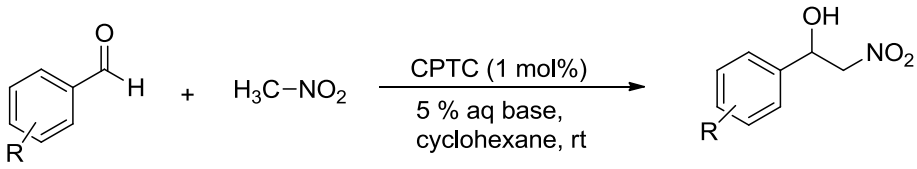
Scheme 3

Haring et al (2016) reported the keratin catalyzed Henry reaction between substituted benzaldehydes and nitromethane/nitroethane by using DMSO or H_2O as the solvents **(Scheme 4)**.



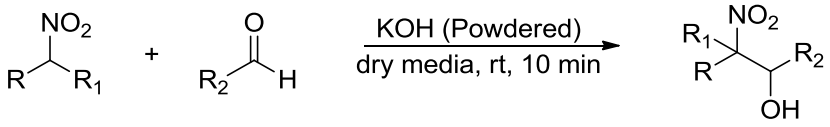
Scheme 4

Vijaya et al (2016) reported the enantioselective Henry reaction of substituted benzaldehydes with nitromethane using chiral phase transfer catalyst (CPTC) in aq/organic solvent media **(Scheme 5)**.



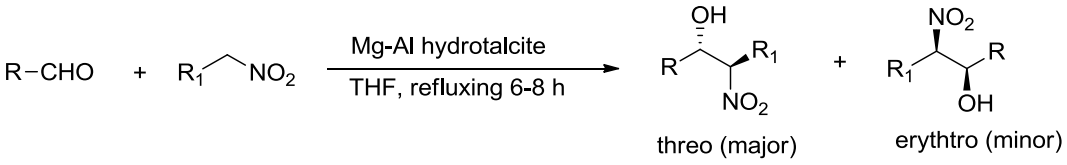
Scheme 5

Ballini and his coworkers (1999) reported the synthesis of β−nitroalkanes through Henry reaction which is catalyzed by stoichiometric amount of powdered KOH in dry media and give the satisfactory yield **(Scheme 6)**.



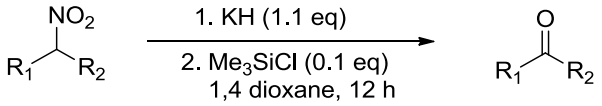
Scheme 6

Bulbule et al (1999) reported the Mg-Al Hydrotalcite catalyzed reaction between aldehydes and nitroalkanes which very efficiently affording the threo–nitroalkanes in a highly diastereoselective manner **(Scheme 7)**.



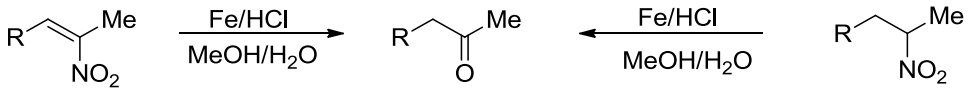
Scheme 7

Hwu and Gilbert (2006) reported the silicon catalyzed Nef reaction. The treatment of secondary nitro compound with potassium hydride followed by addition of chlorotrimethylsilane to the resulted afforded the corresponding ketones **(Scheme 8)**.



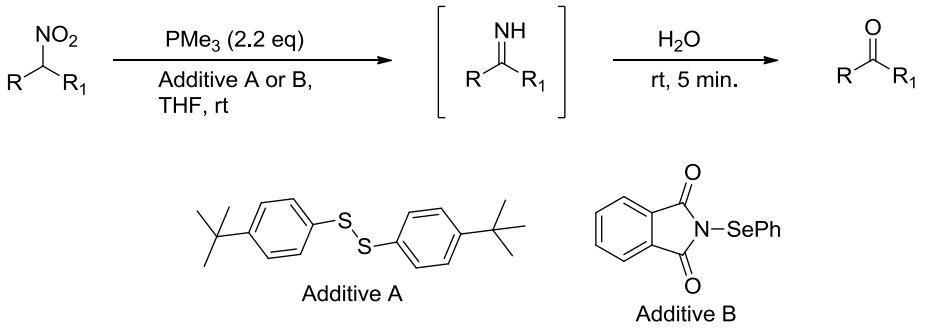
Scheme 8

Pradhan et al (2005) reported the conversion of nitroalkanes or nitroalkenes to ketones by treatment with Fe/HCl in methanol/water as solvent **(Scheme 9)**.



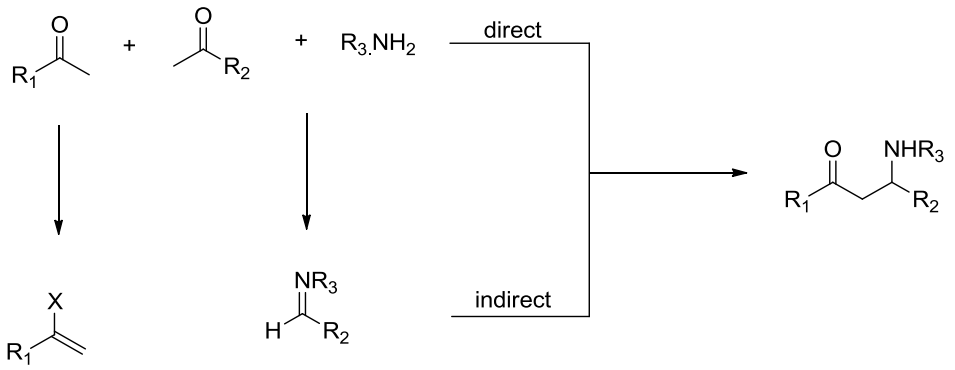
Scheme 9

Bures and Vilarrasa (2008) reported the PMe_3–mediated conversion of secondary nitroalkanes to ketones. The reaction is carried out in commercially available THF solution of PMe_3 at room temperature by the addition of catalyst 4,4-bis-*tert*-butyldiphenyldisulfide or *N*-(phenylselenyl)phthalimide and achived theexcellent yields of corresponding ketones **(Scheme 10)**.



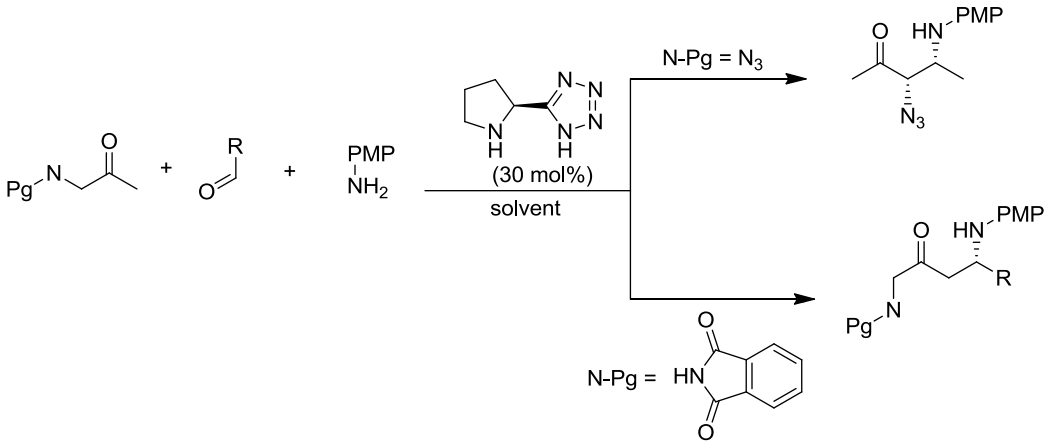
Scheme 10

Benjamin and co-workers (2002) developed proline-catalyzed direct asymmetric three-component Mannich reactions of ketones, aldehydes and amines **(Scheme 11)**.



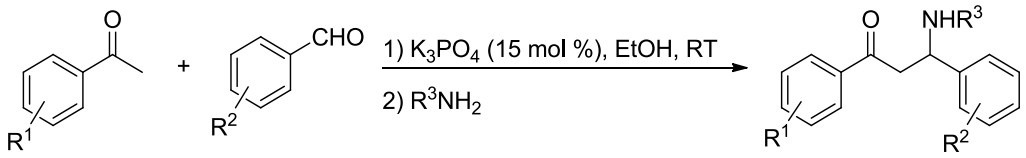
Scheme 11

Chowdari and co-worker (2006) reported that organocatalytic asymmetric Mannich reaction of protected amino ketones with imines in the presence of an L-proline derived tetrazole catalyst afforded diamines with excellent yields and enantioselectivities up to 99 %. The amino ketone protecting group controlled the regioselectivity of the reaction providing access to chiral 1,2-diamines from azido ketones and 1,4-diamines from phthalimido ketones **(Scheme 12)**.



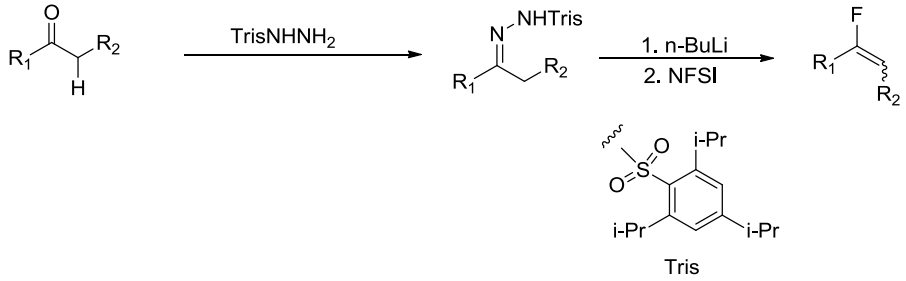
Scheme 12

Movassagh and Khosousi (2012) reported a new strategy for synthesis of β-amino ketones by one-pot reaction of an acetophenone derivative, aryl aldehyde and amine in EtOH at room temperature in the presence of very cheap and very effective catalyst K_3PO_4 **(Scheme 13)**.



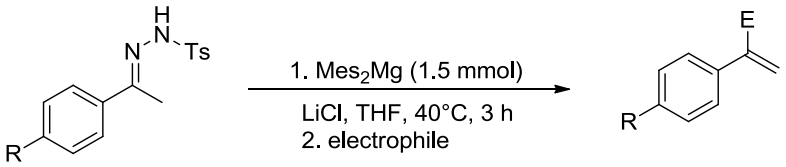
Scheme 13

Yang et al (2013) reported a kind of Shapiro fluorination. Fluoroalkane products can be accessed in one or two step sequence from widely available ketones. This strategy should be useful for the preparation fluorinated analogs of peptide based therapeutics **(Scheme 14)**.



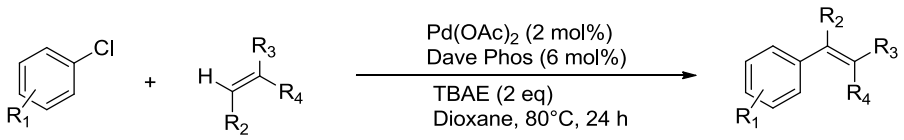
Scheme 14

Kerr et al (2012) reported the bismesitylmagnesium modified Shapiro Reaction. A wide range of tosylhydrazones furnished exceptionally high incorporation of the introduced electrophiles and provide good yield of the functionalized styrenes **(Scheme 15)**.



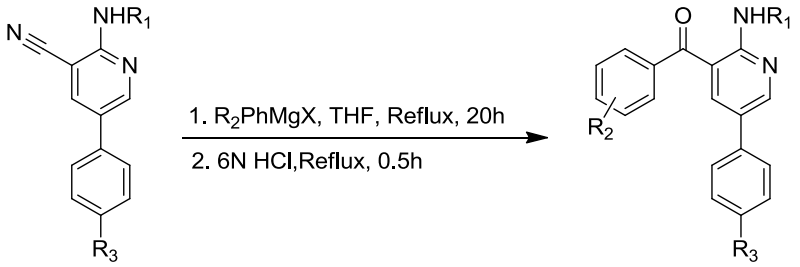
Scheme 15

Xu et al (2011) reported a Pd-Catalyzed Heck reaction of aryl chloride with olefins under mild conditions. High yields of products were achieved with n-$Bu_4N^+OAc^-$ (TBAE) as base, this reaction system tolerates a wide range of olefins **(Scheme 16)**.



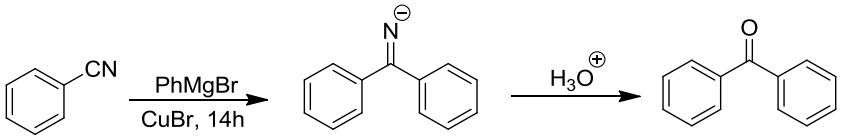
Scheme 16

Hogenkamp et al (2013) reported the reaction of Grignard reagent with 2-amino-5-aryl-3-cyanopyridine which afforded ketone products on hydrolysis **(Scheme 17)**.



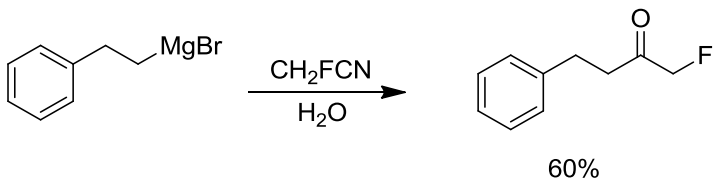
Scheme 17

Weiberth and Hall (1987) promoted the Cu(I) salts catalyzed reaction between phenylmagnesium bromide and benzonitrile which very efficiently affording the benzophenone on hydrolysis **(Scheme 18)**.



Scheme 18

Raja and Klumpp (2011) reported the synthesis of Fluoro-substituted ketones from nitriles in a reasonable yield through the addition of Grignard reagent **(Scheme 19)**.



Scheme 19

5. Technical programme

i) **Name of the experiment**: Synthesis of some novel pyrazole derivatives using 4-formylpyrazoles as scaffold

ii) **Location of study**: Chemistry Lab at Eternal University.

iii) **Methodology**:

a) Source of literature

Chemical abstracts, Indian Journal of Chemistry, Arkivoc, Indian Journal of Heterocyclic Chemistry, Asian Journal of Chemistry, Indian Journal of Pharmaceutical Sciences, Tetrahedron Letters, Tetrahedron, Journal of Indian Chemical Society, Iranian Journal of Pharmaceutical Research, Journal of Brazilian Chemical Society, European Journal of Medicinal Chemistry etc.

b) Pre-laboratory work

The chemicals & reagents required for the synthesis of proposed compounds will be procured from reputed chemical suppliers like Merck, Ranbaxy, Qualigens, Himedia etc.

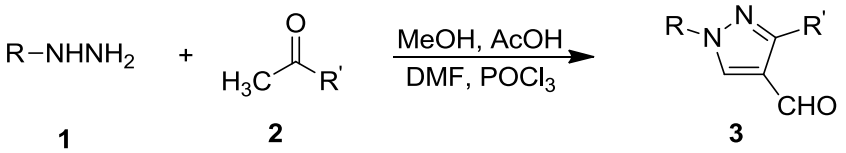
c) Laboratory work

Step 1: Synthesis

It will include standardising the reaction conditions for the synthesis of target compounds. Conventional methods of synthesis will be attempted. The completion of the reaction will be monitored by TLC. Advantages and feasibility of the methods will be analysed.

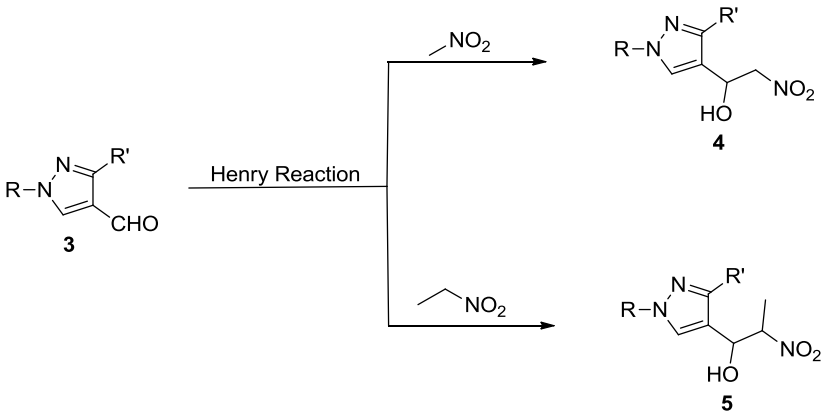
Plan of Work:

i. Synthesis of 4-formylpyrazoles

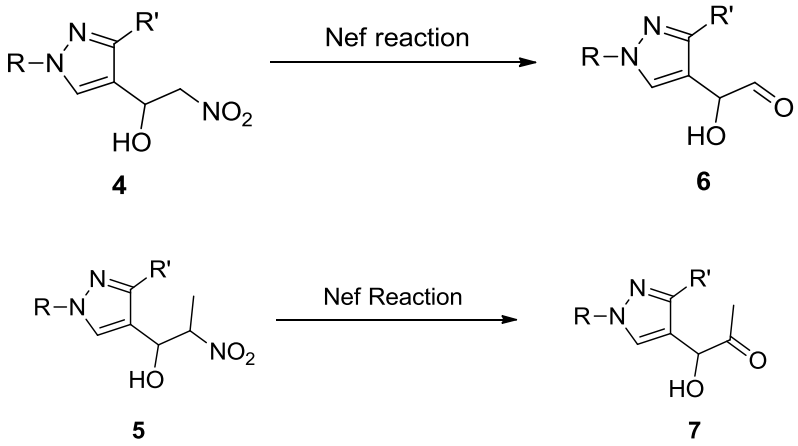


1 2 3

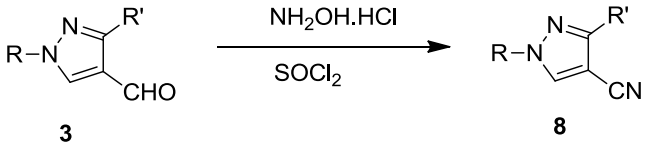
ii. Synthesis of (1,3-disubstituted pyrazol-4-yl)-2-nitroalcohols



iii. Synthesis of (1,3-disubstituted pyrazol-4-yl)-2-hydroxyadehydes/ketones

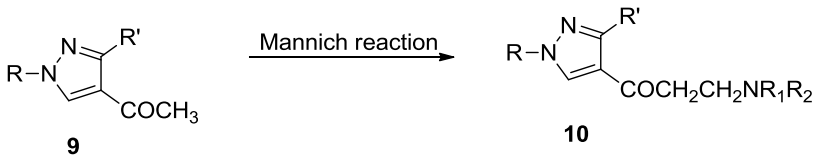


iv. Synthesis of 4-cyanopyrazoles

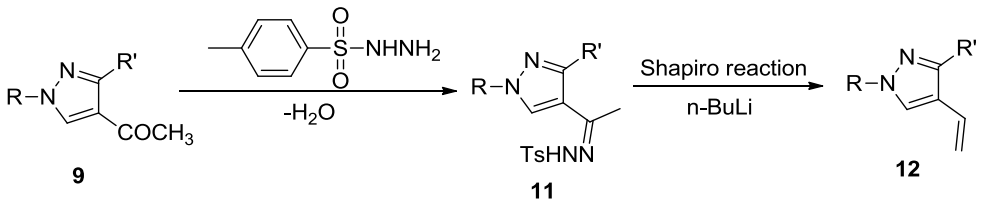


v. Synthesis of (1,3-disubstituted pyrazol-4-yl)ethanone

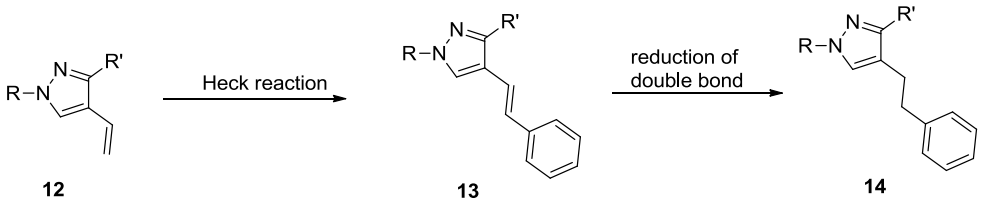
vi. Synthesis of 3-substitutedamino-1-(1,3-disubstitutedpyrazol-4-yl)propan-1-ones



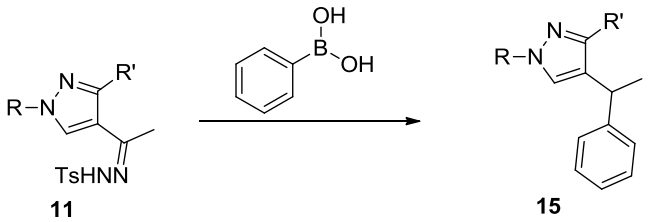
vii. Synthesis of 1,3-disubstituted-4-vinyl-1*H*-pyrazole



viii. Synthesis of 1,3-disubstituted-4-phenethyl-1*H*-pyrazole



ix. Synthesis of 1,3-disubstituted-4-(1-phenylethyl)-1*H*-pyrazole



Step 2: Purification

The synthesized compounds will be purified by different methods like fractional distillation, recrystallization, and column chromatographic methods. The purity will be ascertained by TLC.

Step 3: Characterization

The synthesized compounds will be characterized by:

- Chemical tests for important functional groups.

- With various spectroscopic methods like IR, NMR, MS/LCMS etc.

Observations to be recorded

- State of the compound (solid/liquid)
- If solid, colour of the compound
- Melting point if the compound is solid
- Yield of each compound
- Record and interpretation of IR, NMR, MS and other spectra as per requirements to characterize the desired compound.

6. References

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Candidate Signature